Claims 1-24, 29, 33-34 and 38-39 are pending in the application following entry of the present Amendment. A copy of these claims is enclosed herewith for the Examiner's convenience. Claims 35-37 have been canceled herein without prejudice. Claims 1-3, 8-12, 17-18, 23, 34 and 38-39 have been amended herein to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Support for these amendments are found in the specification as filed and as more fully set forth below. Thus no new matter has been added by way of these amendments.

Amendment to the Application to claim priority under 35 U.S.C. §119(e)

Page 1 of the specification has been amended to add priority claim to the prior International Application No. PCT/US97/22198, filed December 2, 1997 and to U.S. Provisional Application No. 60/032,277, filed on December 2, 1996.

Amendment to the Specification to Correct Typographical Errors

The Examiner has objected to the specification because of an apparent inconsistency regarding the receptor to which SDF binds. On page 11, at line 11, SDF-1 is said to be a ligand of "fusin/CXR4," and at line 26 SDF-1 is said to bind "CCR4." The latter statement wherein SDF-1 is said to bind "CCR4" is a typographical error, and therefore line 26 on page 11 has been amended to recite "stromal cell derived factor-1 (SDF-1) for binding to CXR4." Support for this amendment is found in the specification inter alia on page 11, line 11, and therefore this amendment does not constitute new matter.

Objections to Claims 35-37

The Examiner has objected to claims 35-37 under 37 CFR 1.75 as being a substantial duplicate of claim 1. While not necessarily agreeing to the Examiner's reasoning, but in a good faith effort to expedite the prosecution of the instant application, Applicants have canceled claims 35-37. Since claims 35-37 have been cancelled herein without prejudice, the objections relating to these claims have been rendered moot.

Rejection of claims 1, 2, 5-16, 18-22, 29, 33-35 and 38 under the judicially created doctrine of obviousness-type double patenting

Claims 1, 2, 5-16, 18-22, 29, 33-35 and 38 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting, because in the view of the Examiner, they are unpatentable over claims 3, 6, 8-16, 18-20, 23, 26, 28-36, 38-42, 44-46 and 51 of co-pending Application No. 09/332,275. Applicants will file a Terminal Disclaimer in the co-pending application upon notice that claims 1, 2, 5-16, 18-22, 29, 33, 34 and 38 in the present application are allowable and upon notice in Application No. 09/332,275 that overlapping claims are also allowable.

Rejection of claims 1-24, 29 and 33-39 pursuant to 35 U.S.C. § 112, first paragraph

Claims 1-24, 29 and 33-39 stand rejected under 35 U.S.C. § 112, first paragraph, because in the view of the Examiner, the claims are not enabled. More specifically, the Examiner asserts that the claims are broad and they are not described in the specification in such a way as to enable one of skill in the art to make and/or us the invention. In addition, the Examiner contends that while the relative skill of those in the art of gene therapy is high, the area is unpredictable, and gene therapy methods would require undue experimentation. The Examiner allegedly applying the factors set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), cites the following references in support of the rejection: Verma and Somia (1997, Nature 389:239-242); and Fox (2000, ASM News 66:1-3).

Preliminary, claims 35-37 have been canceled herein thereby rendering the rejection moot as to these claims.

The Examiner cites Verma and Somia (1997, Nature 389:239-242); and Fox (2000, ASM News 66:1-3) to point out the various difficulties and unpredictability associated with gene therapy and in particular *in vivo* gene therapy. While not necessarily agreeing to the Examiner's rejection that the specification does not provide enablement, but in a good faith effort to expedite the prosecution of the instant application, Applicants have amended independent claims 1, 17, 23 and 39. These claims have been amended to restrict the invention for *ex vivo* gene therapy. The remaining claims 2-16, 18-22, 24, 29, 33-34 and 38 depend from the amended independent claims. Thereby Applicants respectfully submit that these claims are enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph, and traverse the rejections of claims 1-24, 29, 33, 34 and 38-39 under 35 U.S.C. § 112, first paragraph, for the reasons set forth below.

It is well-settled that applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required by the statute and are not an end in themselves" (*In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Applicants respectfully contend that the specification as filed is fully enabled for ex *vivo* gene therapy by incorporation of U.S. Patent Application 5,399,346 (Anderson et al., issued March 21, 1995), and attention is directed to the sections which disclose *ex vivo* therapeutic methods (specification, page 34, lines 1-2). An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference. *Ex parte Schwarze*, 151 USPQ 426 (Bd. App. 1966). The Anderson Patent discloses many details of the technique of *ex vivo* gene therapy, including success using *ex vivo* gene therapy with lymphocytes in which a defective adenosine deaminase (ADA) gene is replaced (see, in particular, Example 5 and claim 4). This successful working example, would lead one of skill in the art to believe that they could made and use the claimed invention of the present application.

The Examiner however is of the opinion that the incorporation of the Anderson Patent does not provide support for the pending claims. Specifically, the Examiner asserts that

the Anderson Patent teaches adenosine deaminase (ADA) *ex vivo* gene therapy and that ADA is an enzyme that may show therapeutic effects at a "lower" expression level, and thereby does not provide enablement for the present invention where a higher expression level is allegedly required. By way of the Examiner pointing out that the Anderson Patent teaches ADA *ex vivo* gene therapy, the Examiner in fact agrees that the Anderson Patent does provide enablement for *ex vivo* gene therapy. However, the Examiner opines that the Anderson Patent teaches *ex vivo* gene therapy for only ADA, which is an enzyme with catalytic activity, and therefore is not comparable to the pending claims of "another molecule, which requires a 1:1 stoichiometry (such as binding and retaining proteins intracellulary)."

Applicants respectfully contend that the Anderson Patent does in fact teach *ex vivo* gene therapy for "another molecule" other than ADA. For example, in column 5, lines 22-26, there is disclosure for the expression of "cytokines such as TNF, interleukins, T-cell receptor proteins and Fc receptors for **antigen-binding domains** of antibodies, such as immunoglobulins" to exert a therapeutic effect. Another example for proteins other than ADA is found in column 5 beginning at line 31, where it is recited that "blood cells such as TIL can be modified by introducing a Fab portion of a monoclonal antibody into the cells, thereby enabling the cells to recognize a chosen antigen...suitable genes include genes encoding soluble CD4." Therefore the Anderson Patent discloses *ex vivo* gene therapy for various proteins that the Examiner opines many require a 1:1 stoichiometry as those claimed in the present application. Keeping in mind of course, that the Anderson Patent nowhere discloses Applicants' method of inhibiting HIV coreceptor cell surface expression. Accordingly, Applicants respectfully submit that the specification as filed which includes the incorporation of the Anderson Patent provides enablement for the present invention. For the above reasons, Applicants respectfully request that the rejection of claims be reconsidered and withdrawn.

Rejection of claims 2, 3, 8-12, 18-22 and 34 pursuant to 35 U.S.C. § 112, first paragraph

Claims 2, 3, 8-12, 18-22 and 34 stand rejected under 35 U.S.C. § 112, first paragraph, because in the view of the Examiner, they are not taught by the specification in a such a way as to reasonably convey to one of skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that the recitation of "gene" in these claims lacks written description. Claims 8-12 have

been amended to recite "encoding region" rather than "gene." Claims 2, 3, 18 and 34 have been amended to recite "coding region" rather then "gene." These amendments originate from the Examiner's suggestion (Office Action of April 23, 2002, page 11, lines 3-4), and support is found in the specification on page 11, lines 29-30. This amendment introduces no new matter.

For the above reasons, Applicants respectfully request that the rejection of claims 2, 3, 8-12, 18-22 and 34 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Rejection of claims 8-12 pursuant to 35 U.S.C. § 112, second paragraph

Claims 8-12 stand rejected under 35 U.S.C. § 112, second paragraph, because in the view of the Examiner, they are indefinite for failing to particularly point out and distinctly claim the subject matter, which the applicant regards as the invention. Specifically, the Examiner asserts that claims 8-12 have insufficient antecedent basis in the recitation of the limitation "said chemokine gene." Applicants have amended claims 8-12 to recite "said chemokine encoding region" rather than "said chemokine gene." "Said chemokine encoding region" finds antecedent basis to "a chemokine encoding region" in claim 1. This amendment originates from the Examiner's suggestion (Office Action of April 23, 2002, page 11, lines 3-4), and support is found in the specification on page 11, lines 29-30. Therefore this amendment introduces no new matter.

For the above reasons, Applicants respectfully request that the rejection of claims 8-12 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Summary

The amendments made herein are supported by the specification as filed, and as such, no new matter has been added by way of the present amendments. Applicants respectfully submit that the instant application is in full condition for allowance. Favorable examination of the claims on the merits is respectfully requested.

Respectfully submitted,

CHEN *ET AL.*

April 14, 2003
(Date)

By: _____

KATHRYN DOYLE, PH.D., J.D.
Registration No. 36,317
MORGAN, LEWIS & BOCKIUS, LLP
1701 Market Street
Philadelphia, PA 19103-2921
Telephone: (215) 963-5000
Direct Dial: (215) 963-4723
Facsimile: (215) 963-5001
E-Mail: kdoyle@morganlewis.com
Attorney for Applicants

KD/QDN dep
Enclosures: Marked-up version of the specification to show changes made
Marked-up version of the claims to show changes made
Clean copy of the claims as pending after entry of present Amendment

Marked-Up Copy of Specification

On page 1, before "2. **Description of Related Art**" insert the following paragraph:

-- CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of international patent application PCT/US97/22198, filed December 2, 1997.

This application is entitled to priority pursuant to 35 U.S.C. §119(e) to U.S. provisional patent application 60/032,277, which was filed on December 2, 1996. --

Please delete the paragraph at lines 21-26 on page 1 and insert the following paragraph in place thereof:

The present invention contemplates altering the chemokine receptor ligands so that the ligands may be targeted to the endoplasmic reticulum. These molecules are herein termed intrakines. By "intrakine" is meant any ligand that binds to a C-C chemokine receptor at the cell surface but has been modified to be targeted to the ER of the lymphocyte or other intracellular organelle, such ligands include but are not limited to RANTES, MIP-1α, MIP-1β, for binding to CCR5 and stromal cell derived factor-1 (SDF-1) for binding to ~~CCR4~~CXR4.

Marked-up copy of the claims

Please cancel claims 35-37 and amend claims 1-3, 8-12, 17-18, 23, 34 and 38-39 as follows:

1. (Twice Amended) An expression vector which comprises an expression region, wherein the expression region comprises:

a promoter;

an intracellular retention signal sequence encoding region; and a

chemokine encoding region;

wherein said intracellular retention signal sequence and said chemokine encoding region are expressed from said promoter as a single intrakine transcript~~.~~; and wherein said expression vector is administered to a lymphocyte, a monocyte, a macrophage or a stem cell; and further wherein said lymphocyte, monocyte, macrophage or stem cell is transduced *ex vivo* with said expression vector.

2. (Amended) The expression vector of claim 1, further comprising a ~~gene~~coding region encoding a secreted chemokine.

3. (Amended) The expression vector of claim 2, wherein said ~~gene~~coding region encoding said secreted chemokine is expressed from an internal ribosome entry site.

8. (Twice Amended) The expression vector of claim 1, wherein said chemokine ~~gene~~encoding region encodes a chemokine that binds to a C-C chemokine 5 receptor, a C-C chemokine 3 receptor, a C-C chemokine 1 receptor or a CXR4 receptor.

9. (Twice Amended) The expression vector of claim 1, wherein said chemokine ~~gene~~encoding region encodes a chemokine that binds to a C-C chemokine 5 receptor.

10. (Twice Amended) The expression vector of claim 1, wherein said chemokine ~~gene~~encoding region encodes a chemokine that binds to a C-C chemokine 3 receptor.

11. (Twice Amended) The expression vector of claim 1, wherein said chemokine ~~gene~~encoding region encodes a chemokine that binds to a C-C chemokine 1 receptor.

12. (Twice Amended) The expression vector of claim 1, wherein said chemokine ~~gene~~encoding region encodes a chemokine that binds to a CXR4 receptor.

17. (Twice Amended) ~~A~~An *ex vivo* method of inhibiting phenotypic expression of a chemokine receptor in a cell, wherein the method comprises blocking cell surface expression of said chemokine receptor by binding of said chemokine receptor with an intrakine.

18. (Twice Amended) The method of claim 17, further defined as comprising the steps of:

obtaining a vector comprising a nucleic acid segment encoding a promoter; an intracellular retention signal sequence and a chemokine receptor binding polypeptide ~~gene~~coding region; and

transducing said vector into said cell;

wherein said vector expresses said intracellular retention signal sequence and chemokine receptor binding polypeptide coding region under the transcriptional control of said promoter to produce a fusion polypeptide when transduced into said cell.

23. (Twice Amended) ~~A~~An *ex vivo* method of inhibiting HIV infection of a cell, said method comprising phenotypically knocking out an HIV co-receptor in said cell by binding of said HIV co-receptor with an intrakine, wherein said phenotypic knock-out of said HIV co-receptor in said cell inhibits infection of said cell.

34. (Amended) The method of claim 24, wherein said cell is transduced with a CXC-chemokine ~~gene~~coding region fused to an endoplasmic reticulum (ER)-retention signal to intracellularly block the transport and surface expression of an endogenous CXR4 receptor.

38. (Twice Amended) A composition comprising the expression vector of claim ~~35~~1 and a pharmaceutically acceptable solution.

39. (Twice Amended) A method of increasing white blood cell count in a subject with an HIV infection comprising administering to said subject a pharmaceutical composition comprising a lymphocytes, a monocytes, a macrophages or a stem cells transduced *ex vivo* with ~~a~~the vector of claim 1, thereby increasing white blood cell count in said subject with an HIV infection.